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Dated 3 June 2003

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The **Patent Office**

1/77

Request for grant of a patent

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1. Your reference — **4-32602P1**

2. Patent applicant: **0217636.0** — 30 JUL 2002

31JUL02 E737242-1 000524
P017700 0.00-0217636.0

3. Name, address and postcode of the or of each applicant *(underline all surnames)*

NOVARTIS AG
LICHTSTRASSE 35
4056 BASEL
SWITZERLAND

Patent ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation — **SWITZERLAND** 7125487005

4. Title of invention — **Organic compounds**

5. Name of your agent *(If you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

B.A. YORKE & CO.
CHARTERED PATENT AGENTS
COOMB HOUSE, 7 ST. JOHN'S ROAD
ISLEWORTH
MIDDLESEX TW7 6NH

Patents ADP number *(if you know it)* — **1800001**

6. If you are declaring priority from one ore more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing (day/month/year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing (day/month/year)

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or

b) there is an inventor who is not named as an applicant, or

c) any named applicant is a corporate body.

(see note (d))

Yes

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	45
Claim(s)	4
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	ONE
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature B.A. Yorke & Co. Date **B.A. Yorke & Co.** **30 July 2002**

12. Name and daytime telephone number of person to contact in the United Kingdom **Mrs. E. Cheetham**
020 8560 5847

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ORGANIC COMPOUNDS

The present invention provides pharmaceutical compositions for the treatment of a disease or condition which responds to aromatase inhibition, in particular a proliferative disease, especially a malignant disease such as breast cancer or similar soft tissue endocrine-sensitive cancer, comprising in combination a bisphosphonate and an aromatase inhibitor for simultaneous, sequential or separate use. Also provided is a method of treating a patient suffering from a disease or condition which responds to aromatase inhibition, e.g. involving abnormal bone turnover as a result of the treatment, comprising administering to the patient an effective amount of a bisphosphonate and an effective amount of an aromatase inhibitor.

Bisphosphonates are widely used to inhibit osteoclast activity in a variety of both benign and malignant diseases, which involve excessive or inappropriate bone resorption. These pyrophosphate analogs not only reduce the occurrence of skeletal related events but they also provide patients with clinical benefit and improve survival. Bisphosphonates are able to prevent bone resorption *in vivo*; the therapeutic efficacy of bisphosphonates has been demonstrated in the treatment of osteoporosis, osteopenia, Paget's disease of bone, tumour-induced hypercalcemia (TIH) and, more recently, bone metastases (BM) and multiple myeloma (MM) (for review see Fleisch H 1997 Bisphosphonates clinical. In Bisphosphonates in Bone Disease. From the Laboratory to the Patient. Eds: The Parthenon Publishing Group, New York/London pp 68-163). The mechanisms by which bisphosphonates inhibit bone resorption are still not completely understood and seem to vary according to the bisphosphonates studied. Bisphosphonates have been shown to bind strongly to the hydroxyapatite crystals of bone, to reduce bone turn-over and resorption, to decrease the levels of hydroxyproline or alkaline phosphatase in the blood, and in addition to inhibit the formation, recruitment, activation and the activity of osteoclasts.

Aromatase inhibitors have well-known valuable pharmacological properties. They are useful for the inhibition of estrogen biosynthesis in mammals and the treatment or prevention

of estrogen dependent disorders responsive thereto, such as mammary tumors (breast carcinoma), endometriosis, premature labor and endometrial tumors in females, as well as gynecomastia in males.

It has now been found that surprisingly the administration of a bisphosphonate, zoledronic acid, to rats treated with an aromatase inhibitor, letrozole, offers long term protection against bone loss in the rats.

Accordingly the present invention provides a pharmaceutical composition for treatment of a disease or condition which responds to aromatase inhibition, in particular a proliferative disease, especially a malignant disease, which comprises in combination a bisphosphonate and an aromatase inhibitor for simultaneous, sequential or separate use.

Further the invention provides the use of an aromatase inhibitor for the preparation of a medicament, for use in combination with a bisphosphonate for treatment of a disease or condition which responds to aromatase inhibition, in particular a proliferative disease, especially a malignant disease.

In the alternative the invention provides use of a bisphosphonate for the preparation of a medicament for use in combination with an aromatase inhibitor for treatment of a disease or condition which responds to aromatase inhibition, in particular a proliferative disease, especially a malignant disease.

In a further aspect the invention provides a method of treating a patient suffering from a disease or condition which responds to aromatase inhibition, in particular a proliferative disease, especially a malignant disease, comprising administering to the patient an effective amount of a bisphosphonate and an effective amount of an aromatase inhibitor.

In yet further aspects the invention provides:

(i) A package comprising a bisphosphonate together with instructions for use in combination with an aromatase inhibitor for treatment of a disease or condition which responds to aromatase inhibition, in particular a proliferative disease, especially a malignant disease, or

(ii) A package comprising an aromatase inhibitor together with instructions for use in combination with a bisphosphonate for treatment of a disease or condition which responds to aromatase inhibition, in particular a proliferative disease, especially a malignant disease.

Diseases and conditions which may be treated in accordance with the present invention include any of those diseases/conditions which may be treated using aromatase inhibitors, especially those mentioned hereinbefore and hereinafter, including malignant diseases such as in particular endocrine-dependent breast cancer, like for example hormone receptor positive or hormone receptor unknown advanced or metastatic breast cancer in postmenopausal women. In particular the present invention may be used in the treatment of diseases and conditions in which treatment with an aromatase inhibitor may induce estrogen deprivation, leading to abnormally increased bone turnover or bone loss. In a very preferred embodiment of the present invention, a combination of an aromatase inhibitor with a bisphosphonate is used in the adjuvant therapy of breast cancer, especially in postmenopausal women. Use of bisphosphonate in combination with an aromatase inhibitor advantageously exerts a bone protective effect, and conveniently may permit treatment with higher doses of aromatase inhibitor, or more prolonged treatment with an aromatase inhibitor than would be possible in the absence of bisphosphonate.

Thus in further embodiments the invention includes:

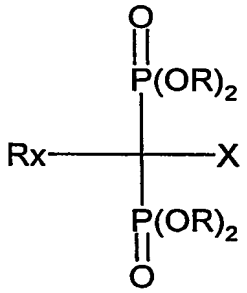
- use of a bisphosphonate to inhibit bone loss during treatment with an aromatase inhibitor;
- use of a bisphosphonate in the manufacture of a medicament for inhibiting bone loss during treatment with an aromatase inhibitor;

- a method of treating of a disease or condition which responds to aromatase inhibition, in particular a proliferative disease, especially a malignant disease, comprising administering an effective amount of an aromatase inhibitor together with an amount of a bisphosphonate effective to inhibit bone loss due to the treatment with an aromatase inhibitor.

Thus in the present description the terms "treatment" or "treat" refer to both prophylactic or preventative treatment as well as curative or disease modifying treatment, including treatment of patients at risk of contracting the disease or suspected to have contracted the disease as well as patients who are ill or have been diagnosed as suffering from a disease or medical condition.

The bisphosphonates for use in the present invention are preferably N-bisphosphonates.

For the purposes of the present description an N-bisphosphonate is a compound which in addition to the characteristic geminal bisphosphate (P-C-P) moiety comprises a nitrogen containing side chain, e.g. a compound of formula I



I

wherein

X is hydrogen, hydroxyl, amino, alkanoyl, or an amino group substituted by C_1-C_4 alkyl, or alkanoyl;

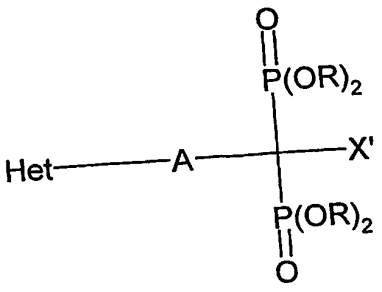
R is hydrogen or C_1-C_4 alkyl and

Rx is a side chain which contains an optionally substituted amino group, or a nitrogen containing heterocycle (including aromatic nitrogen-containing heterocycles),

and pharmaceutically acceptable salts thereof or any hydrate thereof.

Thus, for example, suitable N-bisphosphonates for use in the invention may include the following compounds or a pharmaceutically acceptable salt thereof, or any hydrate thereof: 3-amino-1-hydroxypropane-1,1-diphosphonic acid (pamidronic acid), e.g. pamidronate (APD); 3-(N,N-dimethylamino)-1-hydroxypropane-1,1-diphosphonic acid, e.g. dimethyl-APD; 4-amino-1-hydroxybutane-1,1-diphosphonic acid (alendronic acid), e.g. alendronate; 1-hydroxy-3-(methylpentylamino)-propylidene-bisphosphonic acid, ibandronic acid, e.g. ibandronate; 6-amino-1-hydroxyhexane-1,1-diphosphonic acid; 3-(N-methyl-N-n-pentylamino)-1-hydroxypropane-1,1-diphosphonic acid, e.g. methyl-pentyl-APD (= BM 21.0955); 1-hydroxy-2-(imidazol-1-yl)ethane-1,1-diphosphonic acid, e.g. zoledronic acid; 1-hydroxy-2-(3--pyridyl)ethane-1,1-diphosphonic acid (risedronic acid), e.g. risedronate, including N-methyl pyridinium salts thereof, for example N-methyl pyridinium iodides such as NE-10244 or NE-10446; 3-[N-(2-phenylthioethyl)-N-methylamino]-1-hydroxypropane-1,1-diphosphonic acid; 1-hydroxy-3-(pyrrolidin-1-yl)propane-1,1-diphosphonic acid, e.g. EB 1053 (Leo); 1-(N-phenylaminothiocarbonyl)methane-1,1-diphosphonic acid, e.g. FR 78844 (Fujisawa); 5-benzoyl-3,4-dihydro-2H-pyrazole-3,3-diphosphonic acid tetraethyl ester, e.g. U-81581 (Upjohn); and 1-hydroxy-2-(imidazo[1,2-a]pyridin-3-yl)ethane-1,1-diphosphonic acid, e.g. YM 529.

In one embodiment a particularly preferred N-bisphosphonate for use in the invention comprises a compound of Formula II



II

wherein

Het is an imidazole, oxazole, isoxazole, oxadiazole, thiazole, thiadiazole, pyridine, 1,2,3-triazole, 1,2,4-triazole or benzimidazole radical, which is optionally substituted by alkyl, alkoxy, halogen, hydroxyl, carboxyl, an amino group optionally substituted by alkyl or alkanoyl radicals or a benzyl radical optionally substituted by alkyl, nitro, amino or aminoalkyl;

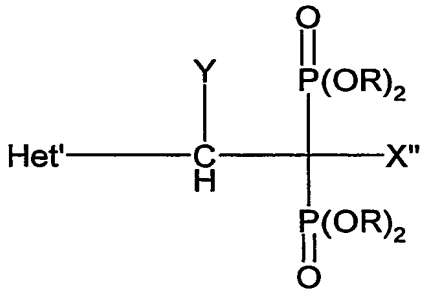
A is a straight-chained or branched, saturated or unsaturated hydrocarbon moiety containing from 1 to 8 carbon atoms;

X' is a hydrogen atom, optionally substituted by alkanoyl, or an amino group optionally substituted by alkyl or alkanoyl radicals, and

R is a hydrogen atom or an alkyl radical,

and the pharmaceutically acceptable salts thereof.

In a further embodiment a particularly preferred bisphosphonate for use in the invention comprises a compound of Formula III



III

wherein

Het' is a substituted or unsubstituted heteroaromatic five-membered ring selected from the group consisting of imidazolyl, imidazolinyl, isoxazolyl, oxazolyl, oxazolinyl, thiazolyl, thiazolinyl, triazolyl, oxadiazolyl and thiadiazolyl wherein said ring can be partly hydrogenated and wherein said substituents are selected from at least one of the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, phenyl, cyclohexyl, cyclohexylmethyl, halogen and amino and wherein two adjacent alkyl substituents of Het can together form a second ring;

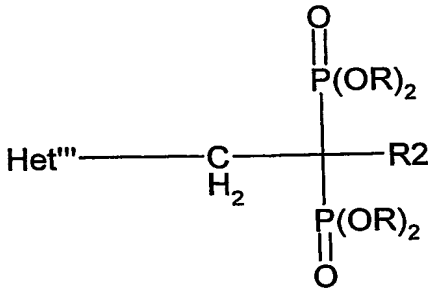
Y is hydrogen or C_1-C_4 alkyl;

X" is hydrogen, hydroxyl, amino, or an amino group substituted by C_1-C_4 alkyl, and

R is hydrogen or C_1-C_4 alkyl;

as well as the pharmaceutically acceptable salts and isomers thereof.

In a yet further embodiment a particularly preferred bisphosphonate for use in the invention comprises a compound of Formula IV



IV

wherein

Het''' is an imidazolyl, 2H-1,2,3-, 1H-1,2,4- or 4H-1,2,4-triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl or thiadiazolyl radical which is unsubstituted or C-mono-or di-substituted by lower alkyl, by lower alkoxy, by phenyl which may in turn be mnon- or disubstituted by lower alkyl, lower alkoxy and/or halogen, by hydroxy, by di-lower alkylamino, by lower alkylthio and/or by halogen and is N-substituted at a substitutable N-atom by lower alkyl or by phenyl-lower alkyl which may in turn be mono- or di-substituted in the phenyl moiety by lower alkyl, lower alkoxy and/or halogen, and

R2 is hydrogen, hydroxy, amino, lower alkylthio or halogen,

lower radicals having up to and including 7 C-atoms,

or a pharmaceutically acceptable salt thereof.

Examples of particularly preferred N-bisphosphonates for use in the invention are:

2-(1-Methylimidazol-2-yl)-1-hydroxyethane-1,1-diphosphonic acid;

2-(1-Benzylimidazol-2-yl)-1-hydroxyethane-1,1-diphosphonic acid;

2-(1-Methylimidazol-4-yl)-1-hydroxyethane-1,1-diphosphonic acid;

1- Amino-2-(1-methylimidazol-4-yl)ethane-1,1-diphosphonic acid;

1- Amino-2-(1-benzylimidazol-4-yl)ethane-1,1-diphosphonic acid;

2-(1-Methylimidazol-2-yl)ethane-1,1-diphosphonic acid;

2-(1-Benzylimidazol-2-yl)ethane-1,1-diphosphonic acid;

2-(Imidazol-1-yl)-1-hydroxyethane-1,1-diphosphonic acid;

2-(Imidazol-1-yl)ethane-1,1-diphosphonic acid;

2-(4H-1,2,4-triazol-4-yl)-1-hydroxyethane-1,1-diphosphonic acid;

2-(Thiazol-2-yl)ethane-1,1-diphosphonic acid;

2-(Imidazol-2-yl)ethane-1,1-diphosphonic acid;

2-(2-Methylimidazol-4(5)-yl)ethane-1,1-diphosphonic acid;

2-(2-Phenylimidazol-4(5)-yl)ethane-1,1-diphosphonic acid;

2-(4,5-Dimethylimidazol-1-yl)-1-hydroxyethane-1,1-diphosphonic acid; and

2-(2-Methylimidazol-4(5)-yl)-1-hydroxyethane-1,1-diphosphonic acid;

and pharmaceutically acceptable salts thereof.

The most preferred N-bisphosphonate for use in the invention is 2-(imidazol-1yl)-1-hydroxyethane-1,1-diphosphonic acid (zoledronic acid) or a pharmaceutically acceptable salt thereof.

All the N-bisphosphonic acid derivatives mentioned above are well known from the literature. This includes their manufacture (see e.g. EP-A-513760, pp. 13-48). For example, 3-amino-1-hydroxypropane-1,1-diphosphonic acid is prepared as described e.g. in US patent 3,962,432 as well as the disodium salt as in US patents 4,639,338 and 4,711,880, and 1-hydroxy-2-(imidazol-1-yl)ethane-1,1-diphosphonic acid is prepared as described e.g. in US patent 4,939,130. See also US patents 4,777,163 and 4,687,767.

The N-bisphosphonates may be used in the form of an isomer or of a mixture of isomers where appropriate, typically as optical isomers such as enantiomers or diastereoisomers or geometric isomers, typically cis-trans isomers. The optical isomers are obtained in the form of the pure antipodes and/or as racemates.

The N-bisphosphonates can also be used in the form of their hydrates or include other solvents used for their crystallisation.

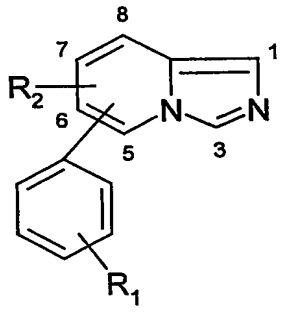
Thus, for example, suitable aromatase inhibitors for use in the invention may include the following compounds or derivatives thereof or pharmaceutically acceptable salts thereof, or any hydrate or solvate thereof: steroids, especially exemestane and formestane and, in particular, non-steroids, especially aminoglutethimide, vorozole, fadrozole, anastrozole and, very especially, letrozole. Further suitable aromatase inhibitors for use in the present invention are roglethimide, pyridoglutethimide, trilostane, testolactone, atamestane, 1-methyl-1,4-androstadiene-3,17-dione, ketokonazole (see also Cancer-Treat-Res.: 94, 231-254, 1998 and WO 99/30708) and YM511 (K.M. Susaki et al. J. Steroid. Biochem. Molec. Biol. 58, 189-194, 1996) or derivatives thereof or pharmaceutically acceptable salts thereof, or any hydrate or solvate thereof. Preferably, an aromatase inhibitor is selected from exemestane, formestane, aminoglutethimide, fadrozole, anastrozole and letrozole. Exemestane can be administered, e.g., in the form as it is marketed, e.g. under the trademark AROMASIN™. Formestane can be administered, e.g., in the form as it is marketed, e.g. under the trademark LENTARON™. Fadrozole can be administered, e.g., in the form as it is marketed, e.g. under the trademark AFEMA™. Anastrozole can be administered, e.g., in the form as it is marketed, e.g. under the trademark ARIMIDEX™. Letrozole can be administered, e.g., in the form as it is marketed, e.g. under the trademark FEMARA™ or FEMAR™. Aminoglutethimide can be administered, e.g., in the form as it is marketed, e.g. under the trademark ORIMETEN™.

Furthermore, the structure of the active agents mentioned herein by name may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g. Patents International (e.g. IMS World Publications). The corresponding content thereof is hereby incorporated by reference. Any person skilled in the art is fully enabled, based on these references, to manufacture and test the pharmaceutical indications and properties in standard test models/methods, both *in vitro* and *in vivo*.

Standard test methods to measure aromatase inhibitory activity of a compound *in vitro* and *in vivo* are well known in the art [see e.g.: J. Biol. Chem. 249, 5364 (1974); J. Enzyme Inhib. 4, 169 (1990) and J. Enzyme Inhib. 4, 179 (1990)].

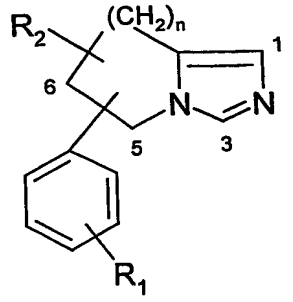
The following compounds and groups of compounds listed below under (a) to (z) and (aa) to (ae) represent further aromatase inhibitors. Each individual group forms a group of aromatase inhibitors that can be used in accordance with the present invention.

(a) The compounds of formulae I and I* as defined in EP-A-165 904. These are especially the compounds of formula I



(I)

wherein R_1 is hydrogen, lower alkyl; lower alkyl substituted by hydroxy, lower alkoxy, lower alkanoyloxy, lower alkanoyl, amino, lower alkylamino, di-lower alkylamino, halogen, sulfo, carboxy, lower alkoxycarbonyl, carbamoyl or by cyano; nitro, halogen, hydroxy, lower alkoxy, lower alkanoyloxy, phenylsulfonyloxy, lower alkylsulfonyloxy, mercapto, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, lower alkanoylthio, amino, lower alkylamino, di-lower alkylamino, lower alkyleneamino, N-morpholino, N-thiomorpholino, N-piperazino that is unsubstituted or lower alkyl-substituted in the 4-position, tri-lower alkylammonio, sulfo, lower alkoxysulfonyl, sulfamoyl, lower alkylsulfamoyl, di-lower alkylsulfamoyl, formyl; iminomethyl that is unsubstituted or substituted at the nitrogen atom by hydroxy, lower alkoxy, lower alkanoyloxy, lower alkyl, phenyl or by amino; C_2-C_7alkanoyl, benzoyl, carboxy, lower alkoxycarbonyl, carbamoyl, lower alkylcarbamoyl, di-lower alkylcarbamoyl, cyano, 5-tetrazolyl, unsubstituted or lower alkyl-substituted 4,5-dihydro-2-oxazolyl or hydroxycarbamoyl; and R_2 is hydrogen, lower alkyl, phenyl-lower alkyl, carboxy-lower alkyl, lower alkoxycarbonyl-lower alkyl, halogen, hydroxy, lower alkoxy, lower alkanoyloxy, mercapto, lower alkylthio, phenyl-lower alkylthio, phenylthio, lower alkanoylthio, carboxy, lower alkoxycarbonyl or lower alkanoyl; the 7,8-dihydro derivatives thereof; and the compounds of formula I*



(I*)

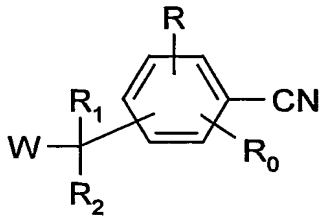
wherein n is 0, 1, 2, 3 or 4; and R_1 and R_2 are as defined above for formula I; it being possible for the phenyl ring in the radicals phenylsulfonyloxy, phenyliminomethyl, benzoyl, phenyl-lower alkyl, phenyl-lower alkylthio and phenylthio to be unsubstituted or substituted by lower alkyl, lower alkoxy or by halogen; it being possible in a compound of formula I* for the two substituents C_6H_4-R_1 and R_2 to be linked to each of the saturated carbon atoms of the saturated ring, either both to the same carbon atom or both to different carbon atoms, and pharmaceutically acceptable salts thereof.

Preferred compounds of this group are:

(1) 5-(p-cyanophenyl)imidazo[1,5-a]pyridine,
(2) 5-(p-ethoxycarbonylphenyl)imidazo[1,5-a]pyridine,
(3) 5-(p-carboxyphenyl)imidazo[1,5-a]pyridine,
(4) 5-(p-tert-butylaminocarbonylphenyl)imidazo[1,5-a]pyridine,
(5) 5-(p-ethoxycarbonylphenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine,
(6) 5-(p-carboxyphenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine,
(7) 5-(p-carbamoylphenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine,
(8) 5-(p-tolyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine,
(9) 5-(p-hydroxymethylphenyl)imidazo[1,5-a]pyridine,
(10) 5-(p-cyanophenyl)-7,8-dihydroimidazo[1,5-a]pyridine,
(11) 5-(p-bromophenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine,
(12) 5-(p-hydroxymethylphenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine,
(13) 5-(p-formylphenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine,
(14) 5-(p-cyanophenyl)-5-methylthio-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine,
(15) 5-(p-cyanophenyl)-5-ethoxycarbonyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine,
(16) 5-(p-aminophenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine,

(17) 5-(p-formylphenyl)imidazo[1,5-a]pyridine,
(18) 5-(p-carbamoylphenyl)imidazo[1,5-a]pyridine,
(19) 5H-5-(4-tert-butylaminocarbonylphenyl)-6,7-dihydropyrrolo[1,2-c]imidazole,
(20) 5H-5-(4-cyanophenyl)-6,7-dihydropyrrolo[1,2-c]imidazole,
(21) 5H-5-(4-cyanophenyl)-6,7,8,9-tetrahydroimidazo[1,5-a]azepine,
(22) 5-(4-cyanophenyl)-6-ethoxycarbonylmethyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine,
(23) 5-(4-cyanophenyl)-6-carboxymethyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine,
(24) 5-benzyl-5-(4-cyanophenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine,
(25) 7-(p-cyanophenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine,
(26) 7-(p-carbamoylphenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine,
(27) 5-(p-cyanophenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine (=fadrozole).

(b) The compounds of formula I as defined in EP-A 236 940. These are especially the compounds of formula I



(I)

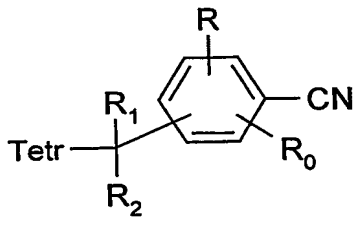
wherein R and R_0, independently of one another, are each hydrogen or lower alkyl, or R and R_0 at adjacent carbon atoms, together with the benzene ring to which they are bonded, form a naphthalene or tetrahydronaphthalene ring; wherein R_1 is hydrogen, lower alkyl, aryl, aryl-lower alkyl or lower alkenyl; R_2 is hydrogen, lower alkyl, aryl, aryl-lower alkyl, (lower alkyl, aryl or aryl-lower alkyl)-thio or lower alkenyl, or wherein R_1 and R_2 together are lower alkylidene or C_4-C_6alkylene; wherein W is 1-imidazolyl, 1-(1,2,4 or 1,3,4)-triazolyl, 3-pyridyl or one of the mentioned heterocyclic radicals substituted by lower alkyl; and aryl within the context of the above definitions has the following meanings: phenyl that is unsubstituted or substituted by one or two substituents from the group lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, nitro, amino, halogen, trifluoromethyl, cyano, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, lower alkanoyl, benzoyl, lower alkylsulfonyl, sulfamoyl, N-lower alkylsulfamoyl and N,N-di-lower alkylsulfamoyl; also thienyl, indolyl, pyridyl or furyl, or one of the four last-mentioned

heterocyclic radicals monosubstituted by lower alkyl, lower alkoxy, cyano or by halogen; and pharmaceutically acceptable salts thereof.

Preferred compounds of this group are:

(1) 4-[α-(4-cyanophenyl)-1-imidazolylmethyl]-benzonitrile,
(2) 4-[α-(3-pyridyl)-1-imidazolylmethyl]-benzonitrile,
(3) 4-[α-(4-cyanobenzyl)-1-imidazolylmethyl]-benzonitrile,
(4) 1-(4-cyanophenyl)-1-(1-imidazolyl)-ethylene,
(5) 4-[α-(4-cyanophenyl)-1-(1,2,4-triazolyl)methyl]-benzonitrile (=letrozole),
(6) 4-[α-(4-cyanophenyl)-3-pyridylmethyl]-benzonitrile.

(c) The compounds of formula I as defined in EP-A-408 509. These are especially the compounds of formula I



(I)

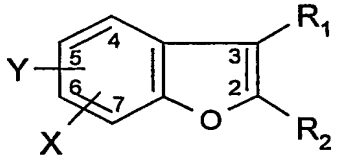
wherein Tetr is 1- or 2-tetrazolyl that is unsubstituted or substituted in the 5-position by lower alkyl, phenyl-lower alkyl or by lower alkanoyl; R_1 and R_2, independently of one another, are each hydrogen; lower alkyl that is unsubstituted or substituted by hydroxy, lower alkoxy, halogen, carboxy, lower alkoxycarbonyl, (amino, lower alkylamino or di-lower alkylamino)-carbonyl or by cyano; lower alkenyl, aryl, heteroaryl, aryl-lower alkyl, C_3-C_6-cycloalkyl, C_3-C_6-cycloalkyl-lower alkyl, lower alkylthio, arylthio or aryl-lower alkylthio; or R_1 and R_2 together are straight-chained C_4-C_6alkylene that is unsubstituted or substituted by lower alkyl, or are a group $-(CH_2)_m$-1,2-phenylene-$(CH_2)_n$- wherein m and n, independently of one another, are each 1 or 2 and 1,2-phenylene is unsubstituted or substituted in the same way as phenyl in the definition of aryl below, or are lower alkylidene that is unsubstituted or mono- or di-substituted by aryl; and R and R_0, independently of one another, are each hydrogen or lower alkyl; or R and R_0 together, located at adjacent carbon atoms of the benzene ring, are a

benzo group that is unsubstituted or substituted in the same way as phenyl in the definition of aryl below; aryl in the above definitions being phenyl that is unsubstituted or substituted by one or more substituents from the group consisting of lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, nitro, amino, halogen, trifluoromethyl, carboxy, lower alkoxycarbonyl, (amino, lower alkylamino or di-lower alkylamino)-carbonyl, cyano, lower alkanoyl, benzoyl, lower alkylsulfonyl and (amino, lower alkylamino or di-lower alkylamino)-sulfonyl; heteroaryl in the above definitions being an aromatic heterocyclic radical from the group consisting of pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furanyl, thienyl, isoxazolyl, oxazolyl, oxadiazolyl, isothiazolyl, thiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidyl, pyrazinyl, triazinyl, indolyl, isoindolyl, benzimidazolyl, benzotriazolyl, benzofuranyl, benzothienyl, benzoxazolyl, benzothiazolyl, benzoxadiazolyl, benzothiadiazolyl, quinolyl and isoquinolyl that is unsubstituted or substituted in the same way as phenyl in the definition of aryl above; and pharmaceutically acceptable salts thereof.

Preferred compounds of this group are:

(1) 4-(2-tetrazolyl)methyl-benzonitrile,
(2) 4-[α-(4-cyanophenyl)-(2-tetrazolyl)methyl]-benzonitrile,
(3) 1-cyano-4-(1-tetrazolyl)methyl-naphthalene,
(4) 4-[α-(4-cyanophenyl)-(1-tetrazolyl)methyl]-benzonitrile.

(d) The compounds of formula I as defined in European Patent Application No.91810110.6. These are especially the compounds of formula I



(I)

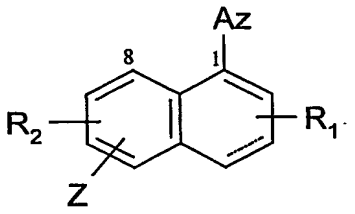
wherein X is halogen, cyano, carbamoyl, N-lower alkylcarbamoyl, N-cycloalkyl-lower alkyl-carbamoyl, N,N-di-lower alkylcarbamoyl, N-arylcarbamoyl, hydroxy, lower alkoxy, aryl-lower alkoxy or aryloxy, wherein aryl is phenyl or naphthyl, each of which is unsubstituted or substituted by lower alkyl, hydroxy, lower alkoxy, halogen and/or by trifluoromethyl; Y is a

group -CH_2-A wherein A is 1-imidazolyl, 1-(1,2,4-triazolyl), 1-(1,3,4-triazolyl), 1-(1,2,3-triazolyl), 1-(1,2,5-triazolyl), 1-tetrazolyl or 2-tetrazolyl, or Y is hydrogen, R_1 and R_2, independently of one another, are each hydrogen, lower alkyl or a group -CH_2-A as defined for Y, or R_1 and R_2 together are -$(CH_2)_n$- wherein n is 3, 4 or 5, with the proviso that one of the radicals Y, R_1 and R_2 is a group -CH_2-A, with the further proviso that in a group -CH_2-A as a meaning of R_1 or R_2, A is other than 1-imidazolyl when X is bromine, cyano or carbamoyl, and with the proviso that in a group -CH_2-A as a meaning of Y, A is other than 1-imidazolyl when X is halogen or lower alkoxy, R_1 is hydrogen and R_2 is hydrogen or lower alkyl, and pharmaceutically acceptable salts thereof.

Preferred compounds of this group are:

(1) 7-cyano-4-[1-(1,2,4-triazolyl)methyl]-2,3-dimethylbenzofuran,
(2) 7-cyano-4-(1-imidazolylmethyl)-2,3-dimethylbenzofuran,
(3) 7-carbamoyl-4-(1-imidazolylmethyl)-2,3-dimethylbenzofuran,
(4) 7-N-(cyclohexylmethyl)carbamoyl-4-(1-imidazolylmethyl)-2,3-dimethylbenzofuran.

(e) The compounds of formula I as defined in Swiss Patent Application 1339/90-7. These are especially the compounds of formula I



(I)

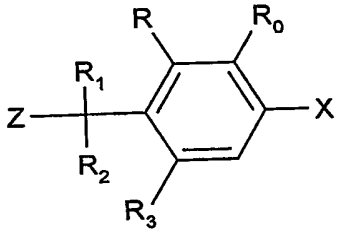
wherein the dotted line denotes an additional bond or no additional bond, Az is imidazolyl, triazolyl or tetrazolyl bonded *via* a ring nitrogen atom, each of those radicals being unsubstituted or substituted at carbon atoms by lower alkyl or by aryl-lower alkyl, Z is carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, N-arylcarbamoyl, cyano, halogen, hydroxy, lower alkoxy, aryl-lower alkoxy, aryloxy, lower alkyl, trifluoromethyl or aryl-lower alkyl, and R_1 and R_2, independently of one another, are each hydrogen, lower alkyl, lower alkoxy, hydroxy, halogen or trifluoromethyl;

aryl being phenyl or naphthyl each of which is unsubstituted or substituted by one or two substituents from the group consisting of lower alkyl, lower alkoxy, hydroxy, halogen and trifluoromethyl; with the proviso that neither Z nor R_2 is hydroxy in the 8-position, and pharmaceutically acceptable salts thereof.

Preferred compounds of this group are:

(1) 6-cyano-1-(1-imidazolyl)-3,4-dihydronaphthalene,
(2) 6-cyano-1-[1-(1,2,4-triazolyl)]-3,4-dihydronaphthalene,
(3) 6-chloro-1-(1-imidazolyl)-3,4-dihydronaphthalene,
(4) 6-bromo-1-(1-imidazolyl)-3,4-dihydronaphthalene.

(f) The compounds of formula I as defined in Swiss Patent Application 3014/90-0. These are especially the compounds of formula I



(I)

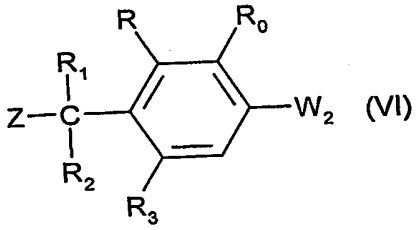
wherein Z is a five-membered nitrogen-containing heteroaromatic ring selected from the group 5-isothiazolyl, 5-thiazolyl, 5-isoxazolyl, 5-oxazolyl, 5-(1,2,3-thiadiazolyl), 5-(1,2,3-oxadiazolyl), 3-(1,2,5-thiadiazolyl), 3-(1,2,5-oxadiazolyl), 4-isothiazolyl, 4-isoxazolyl, 4-(1,2,3-thiadiazolyl), 4-(1,2,3-oxadiazolyl), 2-(1,3,4-thiadiazolyl), 2-(1,3,4-oxadiazolyl), 5-(1,2,4-thiadiazolyl) and 5-(1,2,4-oxadiazolyl); R and R_0 are hydrogen; or R and R_0 together are a benzo group that is unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen or by trifluoromethyl; R_1 is hydrogen, hydroxy, chlorine or fluorine; R_3 is hydrogen; R_2 is hydrogen, lower alkyl or phenyl that is unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen, trifluoromethyl or by cyano; or R_1 and R_2 together are methylidene; or R_2 and R_3 together are $-(CH_2)_3-$; or R_1 and R_2 and R_3 together are a group $=CH-(CH_2)_2-$ wherein the single bond is linked to the benzene ring; X is cyano; and X may also be

halogen when R_2 and R_3 together are $-(CH_2)_3-$ or R_1 and R_2 and R_3 together are a group $=CH-(CH_2)_2-$; and pharmaceutically acceptable salts thereof.

Preferred compounds of this group are:

(1) 4-[α-(4-cyanophenyl)-α-hydroxy-5-isothiazolylmethyl]-benzonitrile,
(2) 4-[α-(4-cyanophenyl)-5-isothiazolylmethyl]-benzonitrile,
(3) 4-[α-(4-cyanophenyl)-5-thiazolylmethyl]-benzonitrile,
(4) 1-(4-cyanophenyl)-1-(5-thiazolyl)-ethylene,
(5) 6-cyano-1-(5-isothiazolyl)-3,4-dihydronaphthalene,
(6) 6-cyano-1-(5-thiazolyl)-3,4-dihydronaphthalene.

(g) The compounds of formula VI as defined in Swiss Patent Application 3014/90-0. These are especially the compounds of formula VI



(VI)

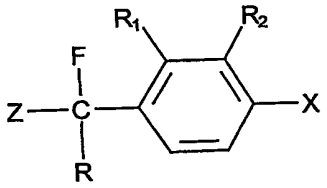
wherein Z is a five-membered nitrogen-containing heteroaromatic ring selected from the group 5-isothiazolyl, 5-thiazolyl, 5-isoxazolyl, 5-oxazolyl, 5-(1,2,3-thiadiazolyl), 5-(1,2,3-oxadiazolyl), 3-(1,2,5-thiadiazolyl), 3-(1,2,5-oxadiazolyl), 4-isothiazolyl, 4-isoxazolyl, 4-(1,2,3-thiadiazolyl), 4-(1,2,3-oxadiazolyl), 2-(1,3,4-thiadiazolyl), 2-(1,3,4-oxadiazolyl), 5-(1,2,4-thiadiazolyl) and 5-(1,2,4-oxadiazolyl); R and R_0 are each hydrogen; or R and R_0 together are a benzo group that is unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen or by trifluoromethyl; R_1 is hydrogen, hydroxy, chlorine or fluorine; R_3 is hydrogen; R_2 is hydrogen, lower alkyl or phenyl that is unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen, trifluoromethyl, aryl-lower alkoxy or by aryloxy; or R_1 and R_2 together are methylidene, and W_2 is halogen, hydroxy, lower alkoxy, aryl-lower alkoxy or aryloxy; aryl in each case being phenyl that is unsubstituted or substituted by lower alkyl,

lower alkoxy, hydroxy, halogen or by trifluoromethyl; and pharmaceutically acceptable salts thereof.

Preferred compounds of this group are:

(1) bis(4,4'-bromophenyl)-(5-isothiazolyl)methanol,
(2) bis(4,4'-bromophenyl)-(5-isothiazolyl)methane,
(3) bis(4,4'-bromophenyl)-(5-thiazolyl)methanol,
(4) bis(4,4'-bromophenyl)-(5-thiazolyl)methane.

(h) The compounds of formula I as defined in Swiss Patent Application 3923/90-4. These are especially the compounds of formula I



(I)

wherein Z is imidazolyl, triazolyl, tetrazolyl, pyrrolyl, pyrazolyl, indolyl, isoindolyl, benzimidazolyl, benzopyrazolyl, benzotriazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazinyl, quinolinyl or isoquinolinyl, all those radicals being bonded *via* their heterocyclic rings and all those radicals being unsubstituted or substituted by lower alkyl, hydroxy, lower alkoxy, halogen or by trifluoromethyl; R_1 and R_2, independently of one another, are each hydrogen or lower alkyl; or R_1 and R_2 together are C_3-C_4alkylene, or a benzo group that is unsubstituted or substituted as indicated below for aryl; R is hydrogen, lower alkyl, aryl or heteroaryl, and X is cyano, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, N,N-lower alkylenecarbamoyl; N,N-lower alkylenecarbamoyl interrupted by -O-, -S- or -NR"-, wherein R" is hydrogen, lower alkyl or lower alkanoyl; N-cycloalkylcarbamoyl, N-(lower alkyl-substituted cycloalkyl)-carbamoyl, N-cycloalkyl-lower alkylcarbamoyl, N-(lower alkyl-substituted cycloalkyl)-lower alkylcarbamoyl, N-aryl-lower alkylcarbamoyl, N-arylcarbamoyl, N-hydroxycarbamoyl, hydroxy, lower alkoxy, aryl-lower alkoxy or aryloxy; and wherein X is also halogen when Z is imidazolyl, triazolyl, tetrazolyl, pyrrolyl, pyrazolyl, indolyl, isoindolyl, benzimidazolyl, benzopyrazolyl or benzotriazolyl;

wherein aryl is phenyl or naphthyl, these radicals being unsubstituted or substituted by from 1 to 4 substituents from the group consisting of lower alkyl, lower alkenyl, lower alkynyl, lower alkylene (linked to two adjacent carbon atoms), C_3-C_8cycloalkyl, phenyl-lower alkyl, phenyl; lower alkyl that is substituted in turn by hydroxy, lower alkoxy, phenyl-lower alkoxy, lower alkanoyloxy, halogen, amino, lower alkylamino, di-lower alkylamino, mercapto, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl and/or by cyano; hydroxy; lower alkoxy, halo-lower alkoxy, phenyl-lower alkoxy, phenoxy, lower alkenyloxy, halo-lower alkenyloxy, lower alkynyloxy, lower alkylenedioxy (linked to two adjacent carbon atoms), lower alkanoyloxy, phenyl-lower alkanoyloxy, phenylcarbonyloxy, mercapto, lower alkylthio, phenyl-lower alkylthio, phenylthio, lower alkylsulfinyl, phenyl-lower alkylsulfinyl, phenylsulfinyl, lower alkylsulfonyl, phenyl-lower alkylsulfonyl, phenylsulfonyl, halogen, nitro, amino, lower alkylamino, C_3-C_8cycloalkylamino, phenyl-lower alkylamino, phenylamino, di-lower alkylamino, N-lower alkyl-N-phenylamino, N-lower alkyl-N-phenyl-lower alkylamino; lower alkyleneamino or lower alkyleneamino interrupted by -O-, -S- or -NR"- (wherein R" is hydrogen, lower alkyl or lower alkanoyl); lower alkanoylamino, phenyl-lower alkanoylamino, phenylcarbonylamino, lower alkanoyl, phenyl-lower alkanoyl, phenylcarbonyl, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, N,N-lower alkylene-carbamoyl; N,N-lower alkylenecarbamoyl interrupted by -O-, -S- or -NR"-, wherein R" is hydrogen, lower alkyl or lower alkanoyl; N-cycloalkylcarbamoyl, N-(lower alkyl-substituted cycloalkyl)-carbamoyl, N-cycloalkyl-lower alkylcarbamoyl, N-(lower alkyl-substituted cycloalkyl)-lower alkylcarbamoyl, N-hydroxycarbamoyl, N-phenyl-lower alkylcarbamoyl, N-phenylcarbamoyl, cyano, sulfo, lower alkoxysulfonyl, sulfamoyl, N-lower alkylsulfamoyl, N,N-di-lower alkylsulfamoyl and N-phenylsulfamoyl; the phenyl groups occurring in the substituents of phenyl and naphthyl in turn being unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen and/or by trifluoromethyl;
wherein heteroaryl is indolyl, isoindolyl, benzimidazolyl, benzopyrazolyl, benzotriazolyl, benzo[b]furanyl, benzo[b]thienyl, benzoxazolyl or benzothiazolyl, those radicals being unsubstituted or substituted by from 1 to 3 identical or different substituents selected from lower alkyl, hydroxy, lower alkoxy, halogen, cyano and trifluoromethyl; and pharmaceutically acceptable salts thereof.

Those compounds are especially the compounds of formula I wherein Z is 1-imidazolyl, 1-(1,2,4-triazolyl), 1-(1,3,4-triazolyl), 1-(1,2,3-triazolyl), 1-tetrazolyl, 2-tetrazolyl, 3-pyridyl, 4-

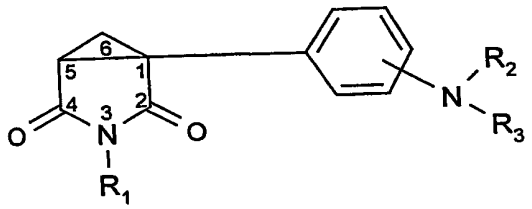
pyridyl, 4-pyrimidyl, 5-pyrimidinyl or 2-pyrazinyl; R_1 and R_2, independently of one another, are each hydrogen or lower alkyl; or R_1 and R_2 together are 1,4-butylene or a benzo group; R is lower alkyl; phenyl that is unsubstituted or substituted by cyano, carbamoyl, halogen, lower alkyl, trifluoromethyl, hydroxy, lower alkoxy or by phenoxy; or benzotriazolyl or benzo[b]-furanyl, the last two radicals being unsubstituted or substituted by from 1 to 3 identical or different substituents selected from lower alkyl, halogen and cyano; and X is cyano or carbamoyl; and wherein X is also halogen when Z is 1-imidazolyl, 1-(1,2,4-triazolyl), 1-(1,3,4-triazolyl), 1-(1,2,3-triazolyl), 1-tetrazolyl or 2-tetrazolyl; and pharmaceutically acceptable salts thereof.

Preferred compounds of this group are:

(1) 4-[α-(4-cyanophenyl)-α-fluoro-1-(1,2,4-triazolyl)methyl]-benzonitrile,
(2) 4-[α-(4-cyanophenyl)-α-fluoro-(2-tetrazolyl)methyl]-benzonitrile,
(3) 4-[α-(4-cyanophenyl)-α-fluoro-(1-tetrazolyl)methyl]-benzonitrile,
(4) 4-[α-(4-cyanophenyl)-α-fluoro-(1-imidazolyl)methyl]-benzonitrile,
(5) 1-methyl-6-[α-(4-chlorophenyl)-α-fluoro-1-(1,2,4-triazolyl)methyl]-benzotriazole,
(6) 4-[α-(4-cyanophenyl)-α-fluoro-1-(1,2,3-triazolyl)methyl]-benzonitrile,
(7) 7-cyano-4-[α-(4-cyanophenyl)-α-fluoro-1-(1,2,4-triazolyl)methyl]-2,3-dimethylbenzo[b]-furan,
(8) 4-[α-(4-bromophenyl)-α-fluoro-1-(1,2,4-triazolyl)methyl]-benzonitrile,
(9) 4-[α-(4-cyanophenyl)-α-fluoro-(5-pyrimidyl)methyl]-benzonitrile,
(10) 4-[α-(4-bromophenyl)-α-fluoro-(5-pyrimidyl)methyl]-benzonitrile,
(11) 4-[α-(4-cyanophenyl)-α-fluoro-(3-pyridyl)methyl]-benzonitrile,
(12) 7-bromo-4-[α-(4-cyanophenyl)-α-fluoro-(1-imidazolyl)methyl]-2,3-dimethylbenzo[b]furan,
(13) 7-bromo-4-[α-(4-cyanophenyl)-α-fluoro-1-(1,2,4-triazolyl)methyl]-2,3-dimethylbenzo-[b]furan,
(14) 4-[α-(4-cyanophenyl)-α-fluoro-(5-pyrimidyl)methyl]-benzonitrile,
(15) 4-[α-(4-bromophenyl)-α-fluoro-(5-pyrimidyl)methyl]-benzonitrile,
(16) 4-[α-(4-cyanophenyl)-1-(1,2,3-triazolyl)methyl]-benzonitrile,
(17) 2,3-dimethyl-4-[α-(4-cyanophenyl)-1-(1,2,4-triazolyl)methyl]-7-cyano-benzo[b]furan,
(18) 4-[α-(4-cyanophenyl)-(5-pyrimidyl)methyl]-benzonitrile,
(19) 4-[α-(4-bromophenyl)-(5-pyrimidyl)methyl]-benzonitrile,

(20) 2,3-dimethyl-4-[α-(4-cyanophenyl)-(1-imidazolyl)methyl]- 7-bromo-benzo[b]furan,
(21) 2,3-dimethyl-4-[α-(4-cyanophenyl)-1-(1,2,4-triazolyl)methyl]-7-bromo-benzo[b]furan.

(i) The compounds of formula I as defined in EP-A-114 033. These are especially the compounds of formula I



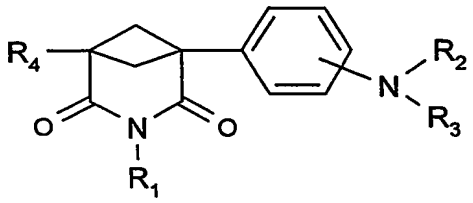
(I)

wherein R_1 is hydrogen, R_2 is hydrogen, sulfo, C_1-C_7alkanoyl or C_1-C_7alkanesulfonyl and R_3 is hydrogen, or wherein R_1 is C_1-C_{12}alkyl, C_2-C_{12}alkenyl, C_2-C_7alkynyl, C_3-C_{10}cycloalkyl, C_3-C_{10}cycloalkenyl, C_3-C_6cycloalkyl-C_1-C_4alkyl, C_3-C_6cycloalkyl-C_2-C_4alkenyl or C_3-C_6cycloalkenyl-C_1-C_4alkyl, R_2 is hydrogen, C_1-C_7alkyl, sulfo, C_1-C_7alkanoyl or C_1-C_7alkanesulfonyl and R_3 is hydrogen or C_1-C_7alkyl, and pharmaceutically acceptable salts of those compounds.

Preferred compounds of this group are:

(1) 1-(4-aminophenyl)-3-methyl-3-azabicyclo[3.1.0]hexane-2,4-dione,
(2) 1-(4-aminophenyl)-3-n-propyl-3-azabicyclo[3.1.0]hexane-2,4-dione,
(3) 1-(4-aminophenyl)-3-isobutyl-3-azabicyclo[3.1.0]hexane-2,4-dione,
(4) 1-(4-aminophenyl)-3-n-heptyl-3-azabicyclo[3.1.0]hexane-2,4-dione,
(5) 1-(4-aminophenyl)-3-cyclohexylmethyl-3-azabicyclo[3.1.0]hexane-2,4-dione.

(j) The compounds of formula I as defined in EP-A-166 692. These are especially the compounds of formula I



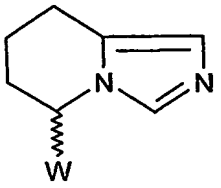
(I)

wherein R_1 is hydrogen, alkyl having from 1 to 12 carbon atoms, alkenyl having from 2 to 12 carbon atoms, lower alkynyl, cycloalkyl or cycloalkenyl each having from 3 to 10 carbon atoms, cycloalkyl-lower alkyl having from 4 to 10 carbon atoms, cycloalkyl-lower alkenyl having from 5 to 10 carbon atoms, cycloalkenyl-lower alkyl having from 4 to 10 carbon atoms, or aryl having from 6 to 12 carbon atoms or aryl-lower alkyl having from 7 to 15 carbon atoms, each of which is unsubstituted or substituted by lower alkyl, hydroxy, lower alkoxy, acyloxy, amino, lower alkylamino, di-lower alkylamino, acylamino or by halogen, R_2 is hydrogen, lower alkyl, sulfo, lower alkanoyl or lower alkanesulfonyl, R_3 is hydrogen or lower alkyl and R_4 is hydrogen, lower alkyl, phenyl or phenyl substituted by $-N(R_2)(R_3)$, and pharmaceutically acceptable salts thereof, radicals described as "lower" containing up to and including 7 carbon atoms.

Preferred compounds of this group are:

(1) 1-(4-aminophenyl)-3-n-propyl-3-azabicyclo[3.1.1]heptane-2,4-dione,
(2) 1-(4-aminophenyl)-3-methyl-3-azabicyclo[3.1.1]heptane-2,4-dione,
(3) 1-(4-aminophenyl)-3-n-decyl-3-azabicyclo[3.1.1]heptane-2,4-dione,
(4) 1-(4-aminophenyl)-3-cyclohexyl-3-azabicyclo[3.1.1]heptane-2,4-dione,
(5) 1-(4-aminophenyl)-3-cyclohexylmethyl-3-azabicyclo[3.1.1]heptane-2,4-dione.

(k) The compounds of formula I as defined in EP-A-356 673. These are especially the compounds of formula I



(I)

wherein W

(α) is a 2-naphthyl or 1-anthryl radical, wherein each benzene ring is unsubstituted or substituted by a substituent selected from halogen, hydroxy, carboxy, cyano and nitro; or

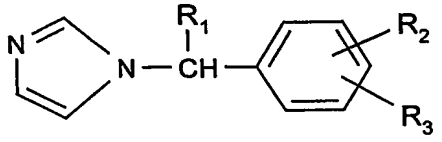
(β) is 4-pyridyl, 2-pyrimidyl or 2-pyrazinyl, each of those radicals being unsubstituted or substituted by a substituent selected from halogen, cyano, nitro, C_1-C_4alkoxy and C_2-C_5-alkoxycarbonyl; and pharmaceutically acceptable salts thereof.

Preferred compounds of this group are:

(1) 5-(2'-naphthyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine,

(2) 5-(4'-pyridyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine.

(l) The compounds of formula I or Ia as defined in EP-A-337 929. These are especially the compounds of formula I/Ia



(I/Ia)

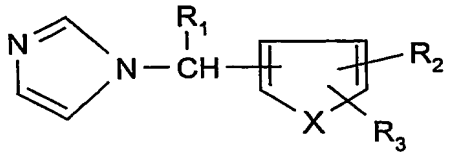
wherein R_1 is hydrogen, methyl, ethyl, propyl, propenyl, isopropyl, butyl, hexyl, octyl, decyl, cyclopentyl, cyclohexyl, cyclopentylmethyl, cyclohexylmethyl or benzyl, R_2 is benzyloxy, 3-bromo-, 4-bromo-, 4-chloro-, 2,3-, 2,4-, 4,5- or 4,6-dichloro-benzyloxy, and R_3 is cyano; C_2-C_{10}alkanoyl that is unsubstituted or mono- or poly-substituted by halogen, methoxy, amino, hydroxy and/or by cyano; benzoyl that is unsubstituted or substituted by one or more substituents from the group halogen, C_1-C_4alkyl, methoxy, amino, hydroxy and cyano;

carboxy, (methoxy, ethoxy or butoxy)-carbonyl, carbamoyl, N-isopropylcarbamoyl, N-phenyl-carbamoyl, N-pyrrolidylcarbonyl, nitro or amino; and pharmaceutically acceptable salts thereof.

Preferred compounds of this group are:

(1) 4-(2,4-dichlorobenzyloxy)-3-[1-(1-imidazolyl)-butyl]-benzonitrile,
(2) (4-(4-bromobenzyloxy)-3-[1-(1-imidazolyl)-butyl]-phenyl pentyl ketone,
(3) 4-(4-bromobenzyloxy)-3-[1-(1-imidazolyl)-butyl]-benzanilide,
(4) 4-(4-bromobenzyloxy)-3-[1-(1-imidazolyl)-butyl]-benzoic acid,
(5) 3-(2,4-dichlorobenzyloxy)-4-[1-(1-imidazolyl)-butyl]-benzonitrile,
(6) 3-(2,4-dichlorobenzyloxy)-4-[1-(1-imidazolyl)-butyl]-benzoic acid methyl ester,
(7) 3-(2,4-dichlorobenzyloxy)-4-[1-(1-imidazolyl)-butyl]-benzoic acid,
(8) 3-(3-bromobenzyloxy)-4-[1-(1-imidazolyl)-butyl]-benzonitrile,
(9) 4-(3-bromobenzyloxy)-3-[1-(1-imidazolyl)-butyl]-benzonitrile,
(10) 3-(4-bromobenzyloxy)-4-[1-(1-imidazolyl)-butyl]-benzoic acid,
(11) 3-(4-bromobenzyloxy)-4-[1-(1-imidazolyl)-butyl]-benzanilide,
(12) 3-(4-bromobenzyloxy)-4-[1-(1-imidazolyl)-butyl]-phenyl pentyl ketone,
(13) 4-(4-bromobenzyloxy)-3-[1-(1-imidazolyl)-butyl]-benzonitrile,
(14) 3-(4-bromobenzyloxy)-4-[1-(1-imidazolyl)-butyl]-benzonitrile,
(15) 4-nitro-2-[1-(1-imidazolyl)-butyl]-phenyl-(2,4-dichlorobenzyl) ether,
(16) 4-amino-2-[1-(1-imidazolyl)-butyl]-phenyl-(2,4-dichlorobenzyl) ether,
(17) (2,4-dichlorobenzyl)-[2-(1-imidazolyl-methyl)-4-nitrophenyl] ether.

(m) The compounds of formula I as defined in EP-A-337 928. These are especially the compounds of formula I



(I)

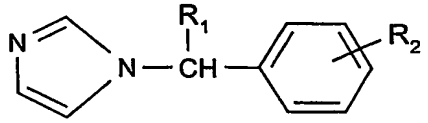
wherein R_1 is hydrogen, methyl, ethyl, propyl, propenyl, isopropyl, butyl, hexyl, octyl, decyl, cyclopentyl, cyclohexyl, cyclopentylmethyl, cyclohexylmethyl or benzyl, R_2 is hydrogen,

halogen, cyano, methyl, hydroxymethyl, cyanomethyl, methoxymethyl, pyrrolidinylmethyl, carboxy, (methoxy, ethoxy or butoxy)-carbonyl, carbamoyl, N-isopropylcarbamoyl, N-phenyl-carbamoyl, N-pyrrolidylcarbonyl; C_2-C_{10}alkanoyl that is unsubstituted or mono- or poly-substituted by halogen, methoxy, ethoxy, amino, hydroxy and/or by cyano; or benzoyl that is unsubstituted or substituted by one or more substituents from the group halogen, C_1-C_4alkyl, methoxy, ethoxy, amino, hydroxy and cyano, R_3 is hydrogen, benzyloxy, 3-bromo-, 4-bromo-, 4-chloro-, 2,3-, 2,4-, 4,5- or 4,6-dichloro-benzyloxy, and X is -CH=N-; -CH=N(-O)- or -S-; and pharmaceutically acceptable salts thereof.

Preferred compounds of this group are:

(1) 5-[1-(1-imidazolyl)-butyl]-thiophene-2-carbonitrile,
(2) 2-[1-(1-imidazolyl)-butyl]-thiophene-4-carbonitrile,
(3) 2-[1-(1-imidazolyl)-butyl]-4-bromo-thiophene,
(4) 2-[1-(1-imidazolyl)-butyl]-5-bromo-thiophene,
(5) 5-[1-(1-imidazolyl)-butyl]-2-thienyl pentyl ketone,
(6) 5-[1-(1-imidazolyl)-butyl]-2-thienyl ethyl ketone,
(7) 5-(4-chlorobenzyloxy)-4-[1-(1-imidazolyl)-pentyl]-pyridine-2-carbonitrile,
(8) 3-(4-chlorobenzyloxy)-4-[1-(1-imidazolyl)-pentyl]-pyridine-2-carbonitrile,
(9) 3-(4-chlorobenzyloxy)-4-[1-(1-imidazolyl)-pentyl]-pyridine-N-oxide,
(10) 3-(4-chlorobenzyloxy)-4-[1-(1-imidazolyl)-pentyl]-pyridine.

(n) The compounds of formula I as defined in EP-A-340 153. These are especially the compounds of formula I



(I)

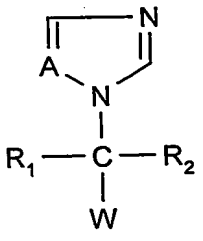
wherein R_1 is hydrogen, methyl, ethyl, propyl, propenyl, isopropyl, butyl, hexyl, octyl, decyl, cyclopentyl, cyclohexyl, cyclopentylmethyl, cyclohexylmethyl or benzyl, and R_2 is a radical from the group methyl, ethyl, propyl, benzyl, phenyl and ethenyl that is substituted by hydroxy, cyano, methoxy, butoxy, phenoxy, amino, pyrrolidinyl, carboxy, lower alkoxy-

carbonyl or by carbamoyl; or R_2 is formyl or derivatised formyl that can be obtained by reaction of the formyl group with an amine or amine derivative from the group hydroxylamine, O-methylhydroxylamine, O-ethylhydroxylamine, O-allylhydroxylamine, O-benzylhydroxylamine, O-4-nitrobenzyloxyhydroxylamine, O-2,3,4,5,6-pentafluorobenzyloxyhydroxylamine, semicarbazide, thiosemicarbazide, ethylamine and aniline; acetyl, propionyl, butyryl, valeryl, caproyl; benzoyl that is unsubstituted or substituted by one or more substituents from the group halogen, C_1-C_4alkyl, methoxy, amino, hydroxy and cyano; carboxy, (methoxy, ethoxy or butoxy)-carbonyl, carbamoyl, N-isopropylcarbamoyl, N-phenylcarbamoyl or N-pyrrolidylcarbonyl; and pharmaceutically acceptable salts thereof.

Preferred compounds of this group are:

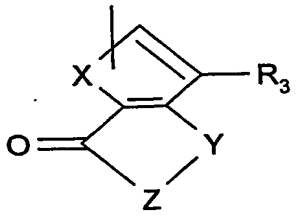
(1) 4-(1-(1-imidazolyl)-butyl)-benzoic acid methyl ester,
(2) 4-(1-(1-imidazolyl)-butyl)-benzoic acid butyl ester,
(3) 4-(1-(1-imidazolyl)-butyl)-phenyl-acetonitrile,
(4) 4-(1-(1-imidazolyl)-butyl)-benzaldehyde,
(5) 4-(1-(1-imidazolyl)-butyl)-benzyl alcohol,
(6) {4-[1-(1-imidazolyl)-butyl]-phenyl}-2-propyl ketone,
(7) 4-[1-(1-imidazolyl)-butyl]-phenyl propyl ketone,
(8) 4-[1-(1-imidazolyl)-butyl]-phenyl butyl ketone,
(9) 4-[1-(1-imidazolyl)-butyl]-phenyl pentyl ketone,
(10) 4-[1-(1-imidazolyl)-butyl]-phenyl hexyl ketone.

(o) The compounds of formula I as defined in DE-A-4 014 006. These are especially the compounds of formula I



(I)

wherein A is an N-atom or a CH radical and W is a radical of the formula

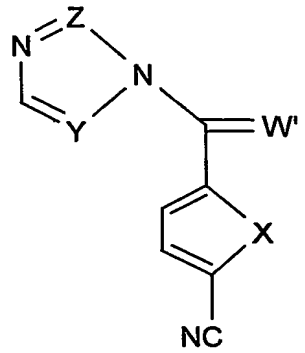


wherein X is an oxygen or a sulfur atom or a -CH=CH- group and Y is a methylene group, an oxygen or a sulfur atom and Z is a $-(CH_2)_n-$ group wherein n = 1, 2 or 3 and either
a) R_3 in W is a hydrogen atom and R_1 and R_2, independently of one another, are each a hydrogen atom, a C_1- to C_{10}alkyl group or a C_3- to C_7cycloalkyl group, or
b) R_2 is as defined under a) and R_1 together with R_3 forms a $-(CH_2)_m-$ group wherein m = 2, 3 or 4,
and their pharmaceutically acceptable addition salts with acids.

Preferred compounds of this group are:

(1) 5-[1-(1-imidazolyl)-butyl]-1-indanone,
(2) 7-[1-(1-imidazolyl)-butyl]-1-indanone,
(3) 6-[1-(1-imidazolyl)-butyl]-1-indanone,
(4) 6-(1-imidazolyl)-6,7,8,9-tetrahydro-1H-benz[e]inden-3(2H)-one,
(5) 2-[1-(1-imidazolyl)-butyl]-4,5-dihydro-6-oxo-cyclopenta[b]-thiophene,
(6) 6-[1-(1-imidazolyl)-butyl]-3,4-dihydro-2H-naphthalen-1-one,
(7) 2-[1-(1-imidazolyl)-butyl]-6,7-dihydro-5H-benzo[b]thiophen-4-one,
(8) 6-[1-(1-imidazolyl)-butyl]-2H-benzo[b]furan-3-one,
(9) 5-[cyclohexyl-(1-imidazolyl)-methyl]-1-indanone,
(10) 2-[1-(1-imidazolyl)-butyl]-4,5-dihydro-6H-benzo[b]thiophen-7-one,
(11) 5-[1-(1-imidazolyl)-1-propyl-butyl]-1-indanone,
(12) 2-[1-(1-imidazolyl)-butyl]-4,5-dihydro-6H-benzo[b]thiophen-7-one,
(13) 2-[1-(1-imidazolyl)-butyl]-4,5-dihydro-6-oxo-cyclopenta[b]-thiophene,
(14) 5-(1-imidazolylmethyl)-1-indanone,
(15) 5-[1-(1,2,4-triazolyl)-methyl]-1-indanone.

(p) The compounds of formula I as disclosed in DE-A-3 926 365. These are especially the compounds of formula I



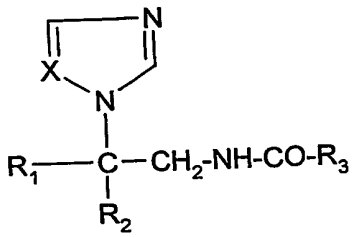
(I)

wherein W' is a cyclopentylidene, cyclohexylidene, cycloheptylidene or 2-adamantylidene radical, X is the grouping -CH=CH-, an oxygen or a sulfur atom, and Y and Z, independently of one another, are each a methine group (CH) or a nitrogen atom, and their pharmaceutically acceptable addition salts with acids.

Preferred compounds of this group are:

(1) 4-[1-cyclohexylidene-1-(imidazolyl)-methyl]-benzonitrile,
(2) 4-[1-cyclopentylidene-1-(imidazolyl)-methyl]-benzonitrile,
(3) 4-[1-cycloheptylidene-1-(imidazolyl)-methyl]-benzonitrile,
(4) 4-[2-adamantylidene-1-(imidazolyl)-methyl]-benzonitrile,
(5) 4-[1-cyclohexylidene-1-(1,2,4-triazolyl)-methyl]-benzonitrile,
(6) 4-[1-cyclopentylidene-1-(1,2,4-triazolyl)-methyl]-benzonitrile,
(7) 4-[1-cycloheptylidene-1-(1,2,4-triazolyl)-methyl]-benzonitrile,
(8) 4-[2-adamantylidene-1-(1,2,4-triazolyl)-methyl]-benzonitrile,
(9) 4-[1-cyclohexylidene-1-(1,2,3-triazolyl)-methyl]-benzonitrile,
(10) 4-[1-cyclopentylidene-1-(1,2,3-triazolyl)-methyl]-benzonitrile,
(11) 5-[cyclohexylidene-1-imidazolylmethyl]-thiophene-2-carbonitrile.

(q) The compounds of formula I as defined in DE-A-3 740 125. These are especially the compounds of formula I



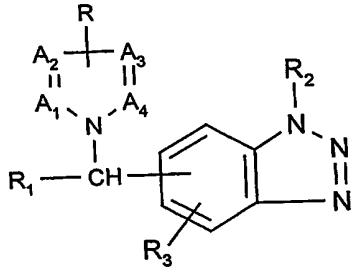
(I)

wherein X is CH or N, R_1 and R_2 are identical or different and are each phenyl or halophenyl, and R_3 is C_1-C_4alkyl; C_1-C_4alkyl substituted by CN, C_1-C_4alkoxy, benzyloxy or by C_1-C_4alkoxy-(mono-, di- or tri-)ethyleneoxy; C_1-C_4alkoxy, phenyl; phenyl that is substituted by halogen or by cyano; a C_5-C_7cycloalkyl group that is optionally condensed by benzene, or is thienyl, pyridyl or 2- or 3-indolyl; and pharmaceutically acceptable acid addition salts thereof.

A preferred compound of this group is:

(1) 2,2-bis(4-chlorophenyl)-2-(1H-imidazol-1-yl)-1-(4-chlorobenzoyl-amino)ethane.

(r) The compounds of formula I as defined in EP-A-293978. These are especially the compounds of formula I



(I),

pharmaceutically acceptable salts and stereochemically isomeric forms thereof, wherein $-A_1=A_2-A_3=A_4-$ is a divalent radical selected from -CH=N-CH=CH-, -CH=N-CH=N- and -CH=N-N=CH-, R is hydrogen or C_1-C_6alkyl; R_1 is hydrogen, C_1-C_{10}alkyl, C_3-C_7cycloalkyl, Ar_1, Ar_2-C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl; R_2 is hydrogen; C_1-C_{10}alkyl that is unsubstituted or substituted by Ar_1; C_3-C_7cycloalkyl, hydroxy, C_1-C_6alkoxy, Ar_1, C_2-C_6alkenyl, C_2-C_6alkynyl,

C_3-C_7cycloalkyl, bicyclo[2.2.1]heptan-2-yl, 2,3-dihydro-1H-indenyl, 1,2,3,4-tetrahydronaphthyl, hydroxy; C_2-C_6alkenyloxy that is unsubstituted or substituted by Ar_2; C_2-C_6alkynyloxy; pyrimidyloxy; di(Ar_2)methoxy, (1-C_1-C_4alkyl-4-piperidinyl)oxy, C_1-C_{10}alkoxy; or C_1-C_{10}alkoxy that is substituted by halogen, hydroxy, C_1-C_6alkyloxy, amino, mono- or di-(C_1-C_6alkyl)amino, trifluoromethyl, carboxy, C_1-C_6alkoxycarbonyl, Ar_1, Ar_2-O-, Ar_2-S-, C_3-C_7cycloalkyl, 2,3-dihydro-1,4-benzodioxinyl, 1H-benzimidazolyl, C_1-C_4alkyl-substituted 1H-benzimidazolyl, (1,1'-biphenyl)-4-yl or by 2,3-dihydro-2-oxo-1H-benzimidazolyl; and R_3 is hydrogen, nitro, amino, mono- or di-(C_1-C_6alkyl)amino, halogen, C_1-C_6alkyl, hydroxy or C_1-C_6alkoxy; wherein Ar_1 is phenyl, substituted phenyl, naphthyl, pyridyl, aminopyridyl, imidazolyl, triazolyl, thienyl, halothienyl, furanyl, C_1-C_6alkylfuranyl, halofuranyl or thiazolyl; wherein Ar_2 is phenyl, substituted phenyl or pyridyl; and wherein "substituted phenyl" is phenyl that is substituted by up to 3 substituents in each case selected independently of one another from the group consisting of halogen, hydroxy, hydroxymethyl, trifluoromethyl, C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_6alkoxycarbonyl, carboxy, formyl, hydroxyiminomethyl, cyano, amino, mono- and di-(C_1-C_6alkyl)amino and nitro.

Preferred compounds of this group are:

(1) 6-[(1H-imidazol-1-yl)-phenylmethyl]-1-methyl-1H-benzotriazole,
(2) 6-[(4-chlorophenyl)(1H-1,2,4-triazol-1-yl)methyl]-1-methyl-1H-benzotriazole.

(s) The compounds of formula II as defined in EP-A-250198, especially

(1) 2-(4-chlorophenyl)-1,1-di(1,2,4-triazol-1-ylmethyl)ethanol,
(2) 2-(4-fluorophenyl)-1,1-di(1,2,4-triazol-1-ylmethyl)ethanol,
(3) 2-(2-fluoro-4-trifluoromethylphenyl)-1,1-di(1,2,4-triazol-1-ylmethyl)ethanol,
(4) 2-(2,4-dichlorophenyl)-1,1-di(1,2,4-triazol-1-ylmethyl)ethanol,
(5) 2-(4-chlorophenyl)-1,1-di(1,2,4-triazol-1-ylmethyl)-ethanol,
(6) 2-(4-fluorophenyl)-1,1-di(1,2,4-triazol-1-yl-methyl)ethanol.

(t) The compounds of formula I as defined in EP-A-281283, especially

(1) (1R*,2R*)-6-fluoro-2-(4-fluorophenyl)-1,2,3,4-tetrahydro-1-(1H-1,2,4-triazol-1-ylmethyl)-naphthalene,

(2) (1R*,2R*)-6-fluoro-2-(4-fluorophenyl)-1,2,3,4-tetrahydro-1-(1H-imidazolylmethyl)naphthalene,
(3) (1R*,2R*)- and (1R*,2S*)-2-(4-fluorophenyl)-1,2,3,4-tetrahydro-1-(1H-1,2,4-triazol-1-ylmethyl)naphthalene-6-carbonitrile,
(4) (1R*,2R*)- and (1R*,2S*)-2-(4-fluorophenyl)-1,2,3,4-tetrahydro-1-(1H-imidazolylmethyl)naphthalene-6-carbonitrile,
(5) (1R*,2R*)- and (1R*,2S*)-1,2,3,4-tetrahydro-1-(1H-1,2,4-triazol-1-ylmethyl)naphthalene-2,6-dicarbonitrile,
(6) (1R*,2R*)- and (1R*,2S*)-1,2,3,4-tetrahydro-1-(1H-imidazol-1-ylmethyl)naphthalene-2,6-dicarbonitrile,
(7) (1R*,2S*)-2-(4-fluorophenyl)-1,2,3,4-tetrahydro-1-(5-methyl-1H-imidazolylmethyl)-naphthalene-6-carbonitrile.

(u) The compounds of formula I as defined in EP-A-296749, especially

(1) 2,2'-[5-(1H-1,2,4-triazol-1-ylmethyl)-1,3-phenylene]di(2-methylpropiononitrile),
(2) 2,2'-[5-(imidazol-1-ylmethyl)-1,3-phenylene]di(2-methylpropiononitrile),
(3) 2-[3-(1-hydroxy-1-methylethyl)-5-(5H-1,2,4-triazol-1-ylmethyl)phenyl]-2-methylpropiononitrile,
(4) 2,2'-[5-dideuterio(1H-1,2,4-triazol-1-yl)methyl-1,3-phenylene]di(2-trideuteriomethyl-3,3,3-trideuteriopropiononitrile),
(5) 2,2'-[5-dideuterio(1H-1,2,4-triazol-1-yl)methyl-1,3-phenylene]di(2-methylpropiononitrile).

(v) The compounds of formula I as defined in EP-A-299683, especially

(1) (Z)-α-(1,2,4-triazol-1-ylmethyl)stilbene-4,4'-dicarbonitrile,
(2) (Z)-4'-chloro-α-(1,2,4-triazol-1-ylmethyl)stilbene-4-carbonitrile,
(3) (Z)-α-(1,2,4-triazol-1-ylmethyl)-4'-(trifluoromethyl)stilbene-4-carbonitrile,
(4) (E)-β-fluoro-α-(1,2,4-triazol-1-ylmethyl)stilbene-4,4'-dicarbonitrile,
(5) (Z)-4'-fluoro-α-(imidazol-1-ylmethyl)stilbene-4-carbonitrile,
(6) (Z)-2',4'-dichloro-α-(imidazol-1-ylmethyl)stilbene-4-carbonitrile,
(7) (Z)-4'-chloro-α-(imidazol-1-ylmethyl)stilbene-4-carbonitrile,

(8) (Z)-α-(imidazol-1-ylmethyl)stilbene-4,4'-dicarbonitrile,

(9) (Z)-α-(5-methylimidazol-1-ylmethyl)stilbene-4,4'-dicarbonitrile,

(10) (Z)-2-[2-(4-cyanophenyl)-3-(1,2,4-triazol-1-yl)propenyl]pyridine-5-carbonitrile.

(w) The compounds of formula I as defined in EP-A-299684, especially

(1) 2-(4-chlorobenzyl)-2-fluoro-1,3-di(1,2,4-triazol-1-yl)propane,

(2) 2-fluoro-2-(2-fluoro-4-chlorobenzyl)-1,3-di(1,2,4-triazol-1-yl)propane,

(3) 2-fluoro-2-(2-fluoro-4-trifluoromethylbenzyl)-1,3-di(1,2,4-triazol-1-yl)propane,

(4) 3-(4-chlorophenyl)-1-(1,2,4-triazol-1-yl)-2-(1,2,4-triazol-1-ylmethyl)butan-2-ol,

(5) 2-(4-chloro-α-fluorobenzyl)-1,3-di(1,2,4-triazol-1-yl)propan-2-ol,

(6) 2-(4-chlorobenzyl)-1,3-bis(1,2,4-triazol-1-yl)propane,

(7) 4-[2-(4-chlorophenyl)-1,3-di(1,2,4-triazol-1-ylmethyl)ethoxymethyl]-benzonitrile,

(8) 1-(4-fluorobenzyl)-2-(2-fluoro-4-trifluoromethylphenyl)-1,3-di(1,2,4-triazol-1-yl)propan-2-ol,

(9) 2-(4-chlorophenyl)-1-(4-fluorophenoxy)-1,3-di(1,2,4-triazol-1-yl)propan-2-ol,

(10) 1-(4-cyanobenzyl)-2-(2,4-difluorophenyl)-1,3-di(1,2,4-triazol-1-yl)propan-2-ol,

(11) 2-(4-chlorophenyl)-1-phenyl-1,3-di(1,2,4-triazol-1-yl)propan-2-ol.

(x) The compounds as defined in claim 1 of EP-A-316097, especially

(1) 1,1-dimethyl-8-(1H-1,2,4-triazol-1-ylmethyl)-2(1H)-naphtho[2,1-b]furanone,

(2) 1,2-dihydro-1,1-dimethyl-2-oxo-8-(1H-1,2,4-triazol-1-ylmethyl)naphtho[2,1-b]furan-7-carbonitrile,

(3) 1,2-dihydro-1,1-dimethyl-2-oxo-8-(1H-1,2,4-triazol-1-ylmethyl)naphtho[2,1-b]furan-7-carboxamide,

(4) 1,2-dihydro-1,1-dimethyl-2-oxo-8-[di(1H-1,2,4-triazol-1-yl)methyl]naphtho[2,1-b]furan-7-carbonitrile.

(y) The compounds of formula I as defined in EP-A-354689, especially

(1) 4-[2-(4-cyanophenyl)-3-(1,2,4-triazol-1-yl)propyl]benzonitrile,

(2) 4-[1-(4-chlorobenzyl)-2-(1,2,4-triazol-1-yl)ethyl]benzonitrile,

(3) 4-[2-(1,2,4-triazol-1-yl)-1-(4-[trifluoromethyl]benzyl)ethyl]benzonitrile,

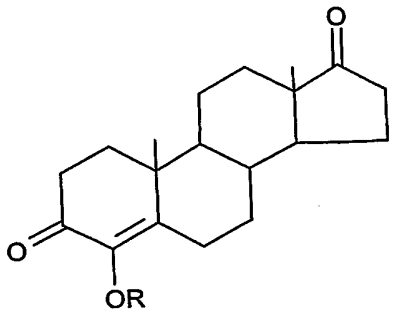
(4) 4-[2-(1,2,4-triazol-1-yl)-1-(4-[trifluoromethoxy]benzyl)ethyl]benzonitrile.

(z) The compounds of formula (1) as defined in EP-A-354683, especially

(1) 6-[2-(4-cyanophenyl)-3-(1,2,4-triazol-1-yl)-propyl]nicotinonitrile,
(2) 4-[1-(1,2,4-triazol-1-yl-methyl)-2-(5-[trifluoromethyl]pyrid-2-yl)ethyl]benzonitrile.

Examples of steroidal aromatase inhibitors that may be mentioned are:

(aa) The compounds of formula I as defined in EP-A-181287. These are especially the compounds of formula I



(I)

wherein R is hydrogen, acetyl, heptanoyl or benzoyl.

A preferred compound of this group is:

(1) 4-hydroxy-4-androstene-3,17-dione.

(ab) The compounds as defined in the claims of US Patent 4322416, especially 10-(2-propynyl)-oestr-4-ene-3,17-dione.

(ac) The compounds as defined in the claims of DE-A-3622841, especially 6-methylene-androsta-1,4-diene-3,17-dione.

(ad) The compounds as defined in the claims of GB-A-2171100, especially 4-amino-androsta-1,4,6-triene-3,17-dione.

Also: (ae) androsta-1,4,6-triene-3,17-dione.

The content of the patent applications mentioned above under (a) to (z) and (aa) to (ad), especially the subgroups of compounds disclosed therein and the individual compounds disclosed therein as examples, as well as the description of the synthesis and the stated pharmaceutical preparations of these compounds, are incorporated herein by reference.

The general terms used to define the aromatase inhibitors mentioned above under (a) to (r) have the following meanings:

Organic radicals designated by the term "lower" contain up to and including 7, preferably up to and including 4, carbon atoms.

Acyl is especially lower alkanoyl.

Aryl is, for example, phenyl or 1- or 2-naphthyl, each of which is unsubstituted or substituted by lower alkyl, hydroxy, lower alkoxy, lower alkanoyloxy, amino, lower alkylamino, di-lower alkylamino, lower alkanoylamino or by halogen.

Any reference hereinbefore and hereinafter to a free bisphosphonate or a free aromatase inhbitor is to be understood as referring also to the corresponding pharmaceutically acceptable salts thereof, as appropriate and expedient.

The aromatase inhibitors can also be used in the form of their hydrates or include other solvents used for their crystallisation.

The most preferred aromatase inhibitor for use in the invention is 4-[α-(4-cyanophenyl)-1-(1,2,4-triazolyl)methyl]-benzonitrile (letrozole) or a pharmaceutically acceptable salt thereof.

Letrozole can be prepared as described in US 5,473,078. It can be administered, e.g., as described in US 4,978,672 or US 5,473,078, or in the form as it is marketed, e.g. under the trademark FEMARA™ or FEMAR™.

Pharmaceutically acceptable salts of bisphosphonates and aromatase inhibitors are preferably salts with bases, conveniently metal salts derived from groups Ia, Ib, IIa and IIb of the Periodic Table of the Elements, including alkali metal salts, e.g. potassium and especially sodium salts, or alkaline earth metal salts, preferably calcium or magnesium salts, and also ammonium salts with ammonia or organic amines.

Especially preferred pharmaceutically acceptable salts of the N-bisphosphonates are those where one, two, three or four, in particular one or two, of the acidic hydrogens of the bisphosphonic acid are replaced by a pharmaceutically acceptable cation, in particular sodium, potassium or ammonium, in first instance sodium.

A very preferred group of pharmaceutically acceptable salts of the N-bisphosphonates is characterized by having one acidic hydrogen and one pharmaceutically acceptable cation, especially sodium, in each of the phosphonic acid groups.

The Agents of the Invention, i.e. the aromatase inhibitor and the bisphosphonate, are preferably used in the form of pharmaceutical preparations that contain the relevant therapeutically effective amount of of each active ingredient (either separately or in combination) optionally together with or in admixture with inorganic or organic, solid or liquid, pharmaceutically acceptable carriers which are suitable for administration. The Agents of the Invention may be present in the same pharmaceutical compositions, though are preferably in separate pharmaceutical compositions. Thus the active ingredients may be administered at the same time (e.g. simultaneously) or at different times (e.g. sequentially) and over different periods of time, which may be separate from one another or overlapping.

The pharmaceutical compositions may be, for example, compositions for enteral, such as oral, rectal, aerosol inhalation or nasal administration, compositions for parenteral, such as intravenous or subcutaneous administration, or compositions for transdermal administration (e.g. passive or iontophoretic).

The particular mode of administration and the dosage may be selected by the attending physician taking into account the particulars of the patient, especially age, weight, life style, activity level, and disease state as appropriate.

The bisphosphonate pharmaceutical compositions may be adapted to oral or parenteral (especially intravenous, intra-arterial or transdermal) administration. Intravenous and oral, first and foremost intravenous, administration is considered to be of particular importance. Preferably the bisphosphonate active ingredient is in a parenteral form, most preferably an intravenous form.

The dosage of the bisphosphonate for use in the invention may depend on various factors, such as effectiveness and duration of action of the active ingredient, mode of administration, sex, age, weight and individual condition of the patient.

Normally the dosage is such that a single dose of the bisphosphonate active ingredient from 0.002 – 20.0 mg/kg, especially 0.01 – 10.0 mg/kg, is administered to a warm-blooded animal weighing approximately 75 kg. If desired, this dose may also be taken in several, optionally equal, partial doses.

"mg/kg" means mg drug per kg body weight of the mammal - including man - to be treated.

The dose mentioned above - either administered as a single dose (which is preferred) or in several partial doses - may be repeated, for example once daily, once weekly, once every

month, or less frequently, e.g. once every three months, once every half year, once every year or more.

Preferably, the bisphosphonates are administered in doses which are in the same order of magnitude as those used in the treatment of the diseases classically treated with bisphosphonic acid derivatives, such as Paget's disease, tumour-induced hypercalcemia or osteoporosis. In other words, preferably the bisphosphonic acid derivatives are administered in doses which would likewise be therapeutically effective in the treatment of Paget's disease, tumour-induced hypercalcaemia or osteoporosis, i.e. preferably they are administered in doses which effectively inhibit bone resorption. For example, for the preferred nitrogen-containing bisphosphonates, e.g. zoledronic acid and salts thereof, doses of bisphosphonate in the range from about 0.5 to about 20 mg, preferably from about 1 to about 10 mg, may be used for treatment of human patients.

Bisphosphonate formulations in single dose unit form contain preferably from about 1% to about 90%, and formulations not in single dose unit form contain preferably from about 0.1% to about 20%, of the active ingredient. Single dose unit forms such as capsules, tablets or dragées contain e.g. from about 1 mg to about 500 mg of the active ingredient.

Preferably, the aromatase pharmaceutical compositions are adapted for oral or parenteral (especially oral) administration. Intravenous and oral, first and foremost oral, adminstration is considered to be of particular importance. Preferably the aromatase inhibitor active ingredient is in oral form.

Similarly the dosage of aromatase inhibitor administered is dependent on the species of warm-blooded animal (mammal), the body weight, age and individual condition, and on the form of administration. The applied dosage of the aromatase inhibitor may range between about 0.001 and 30.0 mg/kg, preferably between about 0.001 to 5 mg/kg.

Aromatase inhibitor formulations in single dose unit form contain preferably from about 1% to about 90%, and formulations not in single dose unit form contain preferably from about

0.1% to about 20%, of the active ingredient. Single dose unit forms such as capsules, tablets or dragées contain e.g. from about 1 mg to about 100 mg of the aromatase inhibitor.

Letrozole is preferably administered daily according to the package insert at a dose of 2.5 mg.

Pharmaceutical preparations comprising Agents of the Invention for enteral and parenteral administration are, for example, those in dosage unit forms, such as dragées, tablets or capsules and also ampoules. They are prepared in a manner known *per se*, for example by means of conventional mixing, granulating, confectioning, dissolving or lyophilising processes. For example, pharmaceutical preparations for oral administration can be obtained by combining the active ingredient with solid carriers, where appropriate granulating a resulting mixture, and processing the mixture or granulate, if desired or necessary after the addition of suitable adjuncts, into tablets or dragée cores.

Other orally administrable pharmaceutical preparations are dry-filled capsules made of gelatin, and also soft, sealed capsules made of gelatin and a plasticiser, such as glycerol or sorbitol. The dry-filled capsules may contain the active ingredient in the form of a granulate, for example in admixture with fillers, such as lactose, binders, such as starches, and/or glidants, such as talc or magnesium stearate, and, where appropriate, stabilisers. In soft capsules the active ingredient is preferably dissolved or suspended in suitable liquids, such as fatty oils, paraffin oil or liquid polyethylene glycols, it being possible also for stabilisers to be added.

Parenteral formulations are especially injectable fluids that are effective in various manners, such as intravenously, intramuscularly, intraperitoneally, intranasally, intradermally or subcutaneously. Such fluids are preferably isotonic aqueous solutions or suspensions which can be prepared before use, for example from lyophilised preparations which contain the active ingredient alone or together with a pharmaceutically acceptable carrier. The pharmaceutical preparations may be sterilised and/or contain adjuncts, for example

preservatives, stabilisers, wetting agents and/or emulsifiers, solubilisers, salts for regulating the osmotic pressure and/or buffers.

Suitable formulations for transdermal application include an effective amount of the active ingredient with carrier. Advantageous carriers include absorbable pharmaceutically acceptable solvents to assist passage through the skin of the host. Characteristically, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the active ingredient of the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

When the combination partners of the present invention are applied in the form as marketed as single drugs, their dosage and mode of administration can take place in accordance with the information provided on the package insert of the respective marketed drug in order to result in the beneficial effect described herein, if not mentioned herein otherwise.

The following examples are intended to illustrate the invention and are not to be construed as being limitations thereon.

EXAMPLES

A. Formulation Examples

Example 1:

Capsules containing coated pellets of active ingredient, for example, disodium pamidronate pentahydrate, as active ingredient:

Core pellet:

active ingredient (ground)	197.3 mg
Microcrystalline cellulose	52.7 mg
(Avicel® PH 105)	250.0 mg

+ Inner coating:	
Cellulose HP-M 603	10.0 mg
Polyethylene glycol	2.0 mg
Talc	8.0 mg
	270.0 mg

+ Gastric juice-resistant outer coating:	
Eudragit® L 30 D (solid)	90.0 mg
Triethyl citrate	21.0 mg
Antifoam® AF	2.0 mg
Water	
Talc	7.0 mg
	390.0 mg

A mixture of disodium pamidronate with Avicel® PH 105 is moistened with water and kneaded, extruded and formed into spheres. The dried pellets are then successively coated in the fluidized bed with an inner coating, consisting of cellulose HP-M 603, polyethylene glycol (PEG) 8000 and talc, and the aqueous gastric juice-resistant coat, consisting of Eudragit® L 30 D, triethyl citrate and Antifoam® AF. The coated pellets are powdered with talc and filled into capsules (capsule size 0) by means of a commercial capsule filling machine, for example Höfliger and Karg.

Example 2:

Monolith adhesive transdermal system, containing as active ingredient, for example, 1-hydroxy-2-(imidazol-1-yl)-ethane-1,1-diphosphonic acid:

Composition:

polyisobutylene (PIB) 300	5.0 g
(Oppanol B1, BASF)	
PIB 35000	3.0 g
(Oppanol B10, BASF)	
PIB 1200000	9.0 g
(Oppanol B100, BASF)	
hydrogenated hydrocarbon resin	43.0 g
(Escorez 5320, Exxon)	
1-dodecylazacycloheptan-2-one	20.0 g
(Azone, Nelson Res., Irvine/CA)	
active ingredient	20.0 g
Total	100.0 g

Preparation:

The above components are together dissolved in 150 g of special boiling point petroleum fraction 100-125 by rolling on a roller gear bed. The solution is applied to a polyester film (Hostaphan, Kalle) by means of a spreading device using a 300 mm doctor blade, giving a coating of about 75 g/m^2. After drying (15 minutes at 60°C), a silicone-treated polyester film (thickness 75 mm, Laufenberg) is applied as the peel-off film. The finished systems are punched out in sizes in the wanted form of from 5 to 30 cm^2 using a punching tool. The complete systems are sealed individually in sachets of aluminised paper.

Example 3:

Vial containing 1.0 mg dry, lyophilized 1-hydroxy-2-(imidazol-1-yl)ethane-1,1-diphosphonic acid (mixed sodium salts thereof). After dilution with 1 ml of water, a solution (concentration 1 mg/ml) for i.v. infusion is obtained.

Composition:

active ingredient (free diphosphonic acid)		1.0 mg
mannitol		46.0 mg
Trisodium citrate x 2 H_2O	ca.	3.0 mg
water		1 ml
water for injection		1 ml .

In 1 ml of water, the active ingredient is titrated with trisodium citrate x 2 H_2O to pH 6.0. Then, the mannitol is added and the solution is lyophilized and the lyophilisate filled into a vial.

Example 4:

Ampoule containing active ingredient, for instance disodium pamidronate pentahydrate dissolved in water. The solution (concentration 3 mg/ml) is for i.v. infusion after dilution.

Composition:

active ingredient	19.73 mg
(≙ 5.0 mg of anhydrous active ingredient)	
mannitol	250 mg
water for injection	5 ml .

Example 5:

Film coated tablets containing 2.5 mg of for example letrozole as active ingredient:

Component	Function	Amount/Tablet (mg)
Core		
Letrozole	Active ingredient	2.50
Colloidal Anhydrous Silica	Glidant	0.5
Microcrystalline Cellulose	Binder (dry)	20.00

Lactose Monohydrate, cryst.	Diluent	61.50
Magnesium Stearate	Lubricant	1.00
Maize Starch	Diluent, disintegrant	9.50
Sodium Starch Glycolate (Sodium Carboxymethyl Starch)	Disintegrant	5.00
Film-Coat		
Methylhydroxypropylcellulose	Film-forming agent	1.838
Iron oxide, yellow	Color pigment	0.249
Polyethylene Glycol 8000	Plasticizer	0.333
Talc, PH	Anti-adhesive and opacifier	1.331
Titanium Dioxide, PH	Pigment and opacifier	0.249
Purified Water*	Coating solvent	qs
Ethanol with 5% Isopropanol*	Coating solvent	qs

*Removed during processing

Preparation:

1. Letrozole is mixed with maize starch in a tumble mixer, screened, mixed and screened again.

2. The pre-mixture is blended in a tumble mixer with screened colloidal anhydrous silica, microcrystalline cellulose, lactose monohydrate and sodium starch glycolate, screened and blended again.

3. After admixing of magnesium stearate the homogeneous tablet mass is compressed into tablets containing the stated amount of active substance.

4. The tablets are coated with a lacquer composed of the excipients stated in the formula above, dissolved or suspended in purified water and small amounts of ethanol with 5% isopropyl alcohol.

Example 6: Intravenous administration of zoledronic acid offers long-term protection against bone loss in rats induced as a consequence of estrogen deprivation

It was investigated whether bone loss induced in rats by either ovariectomy (OVX) or the aromatase inhibitor letrozole (Let) could be prevented by the bisphosphonate zoledronic acid (Zol).

Material and Methods: Adult, skeletally mature, 8-month-old female Wistar rats were assigned to the following treatment groups (n=10): Sham (vehicle), OVX, Let-treated, OVX + Zol and Let + Zol. Zol was injected into the tail vein as a single dose of 0.8, 4 or 20 μg/kg either before OVX or before initiating daily oral dosing of Let (1 mg/kg) for 16 weeks. Changes in cancellous bone mineral density and cortical thickness in the proximal tibia metaphysis were monitored non-invasively by peripheral quantitative computed tomography (pQCT) at 0, 2, 4, 8, 12 and 16 weeks.

Results: Mean cortical thickness decreased continuously and at a similar rate in the OVX and Let groups resulting in a decrease of 22.9 and 21.5% respectively at 16 weeks. In contrast, cancellous bone loss in the Let-group was approximately 50% of the OVX-group at all time-points and was 21.1% (Let) compared to 41.4% (OVX) at 16 weeks. The effect of Zol was dose-dependent with 20 μg/kg fully protecting against both OVX- and Let-induced cancellous bone loss and cortical thinning at all time-points. At 4 μg/kg, the compound was fully protective for up to 8 weeks, but no significant protection against cortical bone loss was observed at 16 weeks in OVX (-18.1%). The protective effect lasted longer in Let-treated rats and was still visible at 16 weeks (-11.5%). Cancellous bone mineral density did not drop significantly for 12 weeks before mild bone loss became apparent in OVX and Let-groups. The lowest Zol dose did not achieve statistically significant protection in any bone compartment at any time-point.

Discussion: Our data indicate for the first time that in rats, Zol dose-dependently protects against cancellous bone loss and cortical thinning induced by daily oral Let. Zol, at a dose of 20 μg/kg, fully protects against Let-induced bone loss for at least 16 weeks. These data support the use of bisphosphonates in general and Zol in particular in preventing or reducing

bone loss in patients undergoing treatment with aromatase inhibitors in general and Let in particular.

CLAIMS

1. A pharmaceutical composition for treatment of a disease or condition which responds to aromatase inhibition which comprises in combination a bisphosphonate and an aromatase inhibitor for simultaneous, sequential or separate use.

2. A pharmaceutical composition according to claim 1 for treatment of a proliferative disease.

3. A method of treating a patient suffering from a disease or condition which responds to aromatase inhibition comprising administering to the patient an effective amount of a bisphosphonate and an effective amount of an aromatase inhibitor.

4. The method of claim 3 for the treatment of a proliferative disease.

5. Use of an aromatase inhibitor for the preparation of a medicament, for use in combination with a bisphosphonate for treatment of a disease or condition which responds to aromatase inhibition.

6. Use of a bisphosphonate for the preparation of a medicament, for use in combination with an aromatase inhibitor for treatment of a disease or condition which responds to aromatase inhibition.

7. The use according to claim 5 or 6 for treatment of a proliferative disease.

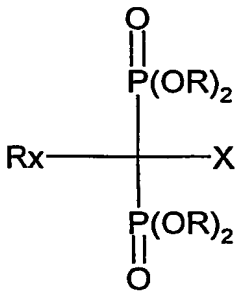
8. A package comprising a bisphosphonate together with instructions for use in combination with an aromatase inhibitor for treatment of a disease or condition which responds to aromatase inhibition, or

a package comprising an aromatase inhibitor together with instructions for use in combination with a bisphosphonate for treatment of a disease or condition which responds to aromatase inhibition.

9. A package according to claim 8 comprising a bisphosphonate together with instructions for use in combination with an aromatase inhibitor for treatment of a proliferative disease, or
a package according to claim 8 comprising an aromatase inhibitor together with instructions for use in combination with a bisphosphonate for treatment of a proliferative disease.

10. A composition according to claim 1 or 2, method according to claim 3 or 4, use according to claim 5, 6 or 7, or package according to claim 8 or 9, in which the bisphosphonate is an N-bisphosphonate.

11. A composition, method, use or package according to claim 10 in which the bisphosphonate is a compound of formula I



I

wherein
X is hydrogen, hydroxyl, amino, alkanoyl, or an amino group substituted by C_1-C_4 alkyl, or alkanoyl;
R is hydrogen or C_1-C_4 alkyl and
Rx is a side chain which contains an optionally substituted amino group, or a nitrogen containing heterocycle (including aromatic nitrogen-containing heterocycles),

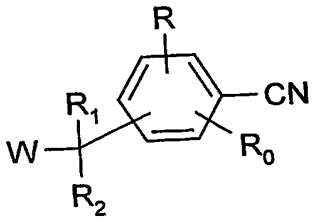
or a pharmaceutically acceptable salt thereof or any hydrate thereof.

12. A composition, method, use or package according to claim 11, in which the bisphosphonate is 2-(imidazol-1yl)-1-hydroxyethane-1,1-diphosphonic acid (zoledronic acid) or a pharmaceutically acceptable salt thereof.

13. A composition according to claim 1 or 2, method according to claim 3 or 4, use according to claim 5, 6 or 7, or package according to claim 8 or 9, in which the aromatase inhibitor is selected from exemestane, formestane, aminoglutethimide, vorozole, fadrozole, anastrozole, letrozole, roglethimide, pyridoglutethimide, trilostane, testolactone, atamestane, 1-methyl-1,4-androstadiene-3,17-dione, ketokonazole and pharmaceutically acceptable salts of these compounds.

14. A composition, method, use or package according to claim 13, in which the aromatase inhibitor is selected from exemestane, formestane, aminoglutethimide, fadrozole, anastrozole, letrozole and pharmaceutically acceptable salts of these compounds.

15. A composition according to claim 1 or 2, method according to claim 3 or 4, use according to claim 5, 6 or 7, or package according to claim 8 or 9, in which the aromatase inhibitor is a compound of formula I



(I)

wherein R and R_0, independently of one another, are each hydrogen or lower alkyl, or R and R_0 at adjacent carbon atoms, together with the benzene ring to which they are bonded, form a naphthalene or tetrahydronaphthalene ring; wherein R_1 is hydrogen, lower alkyl, aryl, aryl-lower alkyl or lower alkenyl; R_2 is hydrogen, lower alkyl, aryl,

aryl-lower alkyl, (lower alkyl, aryl or aryl-lower alkyl)-thio or lower alkenyl, or wherein R_1 and R_2 together are lower alkylidene or C_4-C_6alkylene; wherein W is 1-imidazolyl, 1-(1,2,4 or 1,3,4)-triazolyl, 3-pyridyl or one of the mentioned heterocyclic radicals substituted by lower alkyl; and aryl within the context of the above definitions has the following meanings: phenyl that is unsubstituted or substituted by one or two substituents from the group lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, nitro, amino, halogen, trifluoromethyl, cyano, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, lower alkanoyl, benzoyl, lower alkylsulfonyl, sulfamoyl, N-lower alkylsulfamoyl and N,N-di-lower alkylsulfamoyl; also thienyl, indolyl, pyridyl or furyl, or one of the four last-mentioned heterocyclic radicals monosubstituted by lower alkyl, lower alkoxy, cyano or by halogen; or a pharmaceutically acceptable salt thereof.

16. A composition, method, use or package according to claim 15 in which the aromatase inhibitor is 4-[α-(4-cyanophenyl)-1-(1,2,4-triazolyl)methyl]-benzonitrile (letrozole) or a pharmaceutically acceptable salt thereof.